# Inhibitory Interneuron Progenitor Transplantation Restores Normal Learning and Memory in ApoE4 Knock-In Mice without or with Abeta Accumulation.

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**Public Summary:**
Excitatory and inhibitory balance of neuronal network activity is essential for normal brain function and may be of particular importance to memory. Apolipoprotein (apo) E4 and amyloid-beta (Abeta) peptides, two major players in Alzheimer's disease (AD), cause inhibitory interneuron impairments and aberrant neuronal activity in the hippocampal dentate gyrus in AD-related mouse models and humans, leading to learning and memory deficits. To determine whether replacing the lost or impaired interneurons rescues neuronal signaling and behavioral deficits, we transplanted embryonic interneuron progenitors into the hippocampal hilus of aged apoE4 knock-in mice without or with Abeta accumulation. In both conditions, the transplanted cells developed into mature interneurons, functionally integrated into the hippocampal circuitry, and restored normal learning and memory. Thus, restricted hilar transplantation of inhibitory interneurons restores normal cognitive function in two widely used AD-related mouse models, highlighting the importance of interneuron impairments in AD pathogenesis and the potential of cell replacement therapy for AD. More broadly, it demonstrates that excitatory and inhibitory balance are crucial for learning and memory, and suggests an avenue for investigating the processes of learning and memory and their alterations in healthy aging and diseases.

**Scientific Abstract:**
Excitatory and inhibitory balance of neuronal network activity is essential for normal brain function and may be of particular importance to memory. Apolipoprotein (apo) E4 and amyloid-beta (Abeta) peptides, two major players in Alzheimer's disease (AD), cause inhibitory interneuron impairments and aberrant neuronal activity in the hippocampal dentate gyrus in AD-related mouse models and humans, leading to learning and memory deficits. To determine whether replacing the lost or impaired interneurons rescues neuronal signaling and behavioral deficits, we transplanted embryonic interneuron progenitors into the hippocampal hilus of aged apoE4 knock-in mice without or with Abeta accumulation. In both conditions, the transplanted cells developed into mature interneurons, functionally integrated into the hippocampal circuitry, and restored normal learning and memory. Thus, restricted hilar transplantation of inhibitory interneurons restores normal cognitive function in two widely used AD-related mouse models, highlighting the importance of interneuron impairments in AD pathogenesis and the potential of cell replacement therapy for AD. More broadly, it demonstrates that excitatory and inhibitory balance are crucial for learning and memory, and suggests an avenue for investigating the processes of learning and memory and their alterations in healthy aging and diseases.